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## POLIO IS ALMOST GONE, BUT WILL IT EVER BE?

Eradication plans have been in place for decades // Two vaccines have saved millions of lives // More countries become virus-free each year // But several doors to infection remain wide open.

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# Still a Scourge

■ BY WENDY ORENT

Some of these kids have been vaccinated 10 or 12 times,” says Olen Kew, “and they still get paralytic polio.” For 21 years, Kew, chief of the molecular virology laboratory at the Centers for Disease Control and Prevention in Atlanta, has been involved with the global effort to eradicate polio. His voice cracks in frustration as he recounts the virus’s continued elusiveness even as the campaign, launched by the World Health Assembly in 1988, draws nearer its goal.

Eradicating poliomyelitis has been more difficult and taken more time than almost anyone anticipated. Initially the World Health Assembly set 2000 as the year of eradication. Now the best guess is sometime in 2007. Wild (as opposed to vaccine-derived) poliovirus is circulating in Nigeria, India, Pakistan and Afghanistan, in descending order of known cases. The virus has spread from Nigeria and India to cause renewed infection in formerly polio-free countries. Making eradication all the more difficult, highly evolved oral vaccine-derived polioviruses have been found in several other countries and, in 2005, even spread within one community of unimmunized people in the United States.

Still, the campaign has made dramatic gains. When it began, an estimated 350,000 to 500,000 children per year worldwide were contracting acute flaccid paralysis, and many died. In 2005 there were only about 1,900 cases. China, with more than a fifth of the world's population, has been polio-free since 1994. Bangladesh, Egypt and Niger, where the disease had been widespread, have gone more than a year with no cases. Type 2 poliovirus, one of three serotypes—related yet distinct strains that don't confer cross-immunity—was eradicated in 1999. By most estimates, the quest to rid the planet of polio has saved more than 9 million children.

Yet the poliovirus continues to circulate. And no matter how intently scientists study this foe, many mysteries remain,

## How can polio be associated at once with dirt and cleanliness, with poor and good water systems?

including why epidemic polio has become such a problem in the first place. Though the virus has probably been with us for centuries or millennia—an Egyptian carving dating as far back as 1580 B.C. shows a priest with a withered leg and a dropped foot, suggestive of paralytic polio—there are no records of epidemic paralytic disease before the nineteenth century. And in 1952, only three years before Jonas E. Salk's poliovirus vaccine was approved, more than 57,000 children contracted polio in the United States. Why then? And why does polio, an intestinal virus, produce paralytic disease at all?

In his classic *A History of Poliomyelitis*, Yale epidemiologist John R. Paul makes what has become a well-accepted case for the reason polio reached epidemic proportions during the late nineteenth and early twentieth centuries. Societies were once awash in poliovirus, Paul suggests, and children were exposed as infants, while still protected by maternal antibodies. But beginning in the 1800s, improvements in hygiene, water quality and sewer systems reduced that exposure. As more children failed to develop immunity, terrifying polio epidemics broke out in the United States and Europe.

But if those outbreaks resulted from improved hygiene, why does polio today occur in filthy, crowded locales with high birth rates, poor hygiene and bad water quality? According to Paul's hypothesis, such conditions ought to leave infants exposed to poliovirus at a young, less vulnerable age. So how can polio be associated at once with dirt and cleanliness, with poor and good water systems?

One possibility could be the role of breastfeeding in providing immunity. The maternal antibodies in breast milk lend some protection against infection while it is in the gut, says Eckard Wimmer, a polio virologist at the State University of New York in Stony Brook. Breastfeeding diminishes the chance that the virus will leave a child's intestines and invade

the nervous system. Adults who have been infected with polio have high levels of antibodies, some of which will be passed on through the placenta and the milk of a nursing mother.

Before the nineteenth century, children may well have been exposed to constantly circulating poliovirus while still protected by maternal antibodies—both after birth and through breastfeeding, which often lasted two years or more. But exclusive breastfeeding rates dropped drastically during the late nineteenth and early twentieth centuries, bottoming out during the 1940s and '50s in Western countries. The same thing happened in the developing world, and despite some recent improvement, rates remain low, according to Claire Hajaj of UNICEF. Though it's difficult to prove a link between the decline in breastfeeding and the rise of epidemic polio—and the virus's continued presence in countries where breastfeeding is rare—the timing and what we know about the disease suggest there could be some connection.

But whatever the cause of the outbreaks of epidemic polio in the first half of the twentieth century, it mystified physicians and petrified parents. Summer was

## Will Polio's Threat Always Linger? //

In 2002, using only a gene synthesizer, a chemical bath to turn DNA sequences into RNA, and a genetic sequence that had long been available on the Internet, Eckard Wimmer and a team of researchers at the State University of New York in Stony Brook recreated polio from scratch. "It took us less than two years," says Wimmer. "Soon, with current technological advances," he adds, with only slight exaggeration, "it will take two weeks and a few dollars."

Although some scientists denounced the

exercise as a stunt, Wimmer had a serious purpose—to show that the world will never be truly free from polio. The virus could re-emerge as a bioterrorist threat.

Polio eradication has been modeled upon the campaign against smallpox, which resulted in the worldwide cessation of smallpox vaccination. But illicit stores of that virus may still exist. According to Harvard virologist James Hogle, polio would be less suitable than smallpox as a bioterrorist weapon because of polio's

comparatively low death rate. Yet the relative ease of re-creating poliovirus could make it an ideal agent for maximizing fear and disruption. Polio virologist Vincent Racaniello at Columbia University has estimated that releasing poliovirus into the water supply of a city with an unvaccinated population of 10 million could produce 7,000 cases of paralytic polio. To eliminate such a threat, it may be necessary to continue polio vaccination even after the disease is officially eradicated.

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an especially terrifying time: Swimming pools and even parks were off-limits, and many parents kept their children indoors and away from crowds; you never knew where, or how, the virus might strike. One of the most frightening aspects of polio was its stealth. Unlike smallpox, for example, which left its unmistakable mark on everyone it touched, polio infects as many as 1,000 people for every one who is felled by paralysis.

Poliovirus is an *Enterovirus*, a genus in the picornavirus family of very small, single-stranded RNA viruses. Enteroviruses inhabit the intestines and circulate largely through fecal-oral transmission or in polluted water. Though many cause little disease, a few, such as Enterovirus 71, or several of the Coxsackie viruses, may cause meningitis and occasionally paralysis. But poliovirus is among the most dangerous.

Under an electron microscope, a polio virion (virus particle) appears as a bumpy sphere. Each of the three immunologically unrelated serotypes consists of an RNA genome enclosed in a capsid, or outer shell, by which the virion adheres to human cells via so-called polio receptors. These are found, among other places, on cells of lymphoid tissue lining the digestive tract. According to Harvard virologist James Hogle, the virion uses the receptor as a portal into the cell. There it hijacks the cell's machinery to replicate itself. As long as the infection remains in the gut, however, it's unlikely to harm its human host.

Sometimes, though, this intestinal virus produces paralysis. That, says Hogle, is because poliovirus receptors also exist in nervous tissue, including the anterior horn motor neurons of the brain stem and spinal cord. After it replicates in intestinal cells, the virus can enter the bloodstream, where it causes a mild but noticeable infection. Then it may cross the blood-brain barrier to reach the spinal cord.

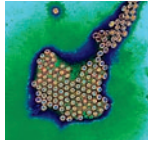


The chance of recovery from paralytic polio, though slim, was about all Americans could hope for when this poster won a 1949 contest sponsored by what would become the March of Dimes. The first polio vaccine hit the market in 1955.

## In the Time of Polio

**1580–1350 B.C.**

An Egyptian stone carving is made of a priest with a shriveled leg and a dropped foot, perhaps the earliest depiction of polio.



**1931**

Frank Macfarlane Burnet and Annie Jean MacNamara identify three immunologically distinct strains of poliovirus: types 1, 2 and 3.



**1952**

During the worst polio year in the United States, more than 57,000 children are paralyzed or die. No one knows why the rate keeps steadily rising or why the “polio season” now extends from Memorial Day through October.

**1961**

The U.S. Public Health Service endorses Albert Sabin’s live vaccine after large-scale immunizations in Eastern Europe. The oral vaccine is easier to administer than Salk’s and proves effective in controlling infections over wide areas.

**1994**

The Western Hemisphere is certified polio-free, though vaccine-derived poliovirus will later be found circulating in Hispaniola and the United States.

**1840**

The first detailed clinical monograph of polio is written by the German orthopedist Jacob von Heine, who deduces that the seat of paralysis must be the patient’s spinal cord.

**1935**

Clinical trials for two vaccines—one killed (inactivated), the other live (attenuated)—prove disastrous. But the Brodie-Park killed strain serves as a prototype for the effective Salk vaccine.



**1953**

A team at the University of Pittsburgh, led by Jonas E. Salk, successfully conducts field trials of their killed vaccine strain. In 1955, the vaccine is approved, and millions of doses are administered that year.



**1988**

The World Health Assembly announces the polio-eradication campaign, resolving to eliminate the disease by the end of 2000 using Sabin’s oral vaccine.

Other times, circulating poliovirus finds a break in muscle tissue, makes its way to nerve cell endings and then shoots up the axons to the motor neurons in the spinal cord or brain stem. According to one theory experimentally proven by Wimmer, injections may sometimes be to blame, giving blood-borne poliovirus increased opportunity to ascend to the motor neurons. Kew believes that tonsillectomies may play a role; these operations, once very common, have been associated with bulbar polio, the most serious form of paralytic disease. Whichever way it gets to the anterior horn motor neurons, the poliovirus destroys them and may cause paralysis or death.

As devastating as the poliovirus can be, for half a century there have been two effective vaccines. The Salk version, approved in 1955, is known as inactivated polio vaccine (IPV). Consisting of a killed strain of the virus, it produces antibodies that circulate in the blood. Children vaccinated with IPV won’t get paralytic disease, though they could develop—and unknowingly pass along—polio-related intestinal infections if exposed to the live poliovirus.

In contrast, the oral polio vaccine (OPV), developed by Albert Sabin and approved in 1961, is made of live, weakened strains of the virus and is designed to produce a mild intestinal infection and induce long-lasting immunity. OPV has been the vaccine of choice for the eradication campaign. Volunteers can drop OPV in a child’s mouth and the infection it produces can spread beyond the vaccinated child to others in the community, widening the impact of a vaccination initiative.

As those on the front lines of the eradication campaign well understand, children in high-risk areas often need more than the usual three doses of oral vaccine to acquire immunity. Even then it doesn’t always work, Kew notes, especially during summer and autumn, polio’s high season. (Cold weather slows transmission of the virus.) Moreover, if a child has diarrhea, the vaccine can pass through the intestines before the live virus strain has a chance to replicate, and malnutrition can prevent antibodies from developing. Both diarrhea and malnutrition are common in Afghanistan, India, Nigeria and



Deployed against an elusive foe, endless doses of oral polio vaccine have been slowly but surely driving out the crippling virus.

Pakistan, where polio has found its last redoubt. What's more, these countries have high birth rates, continually providing a fresh supply of susceptible potential hosts.

Parents may not understand why their children must be vaccinated again and again, nor why, even after multiple vaccinations, a child sometimes develops paralytic polio. These failures lend credence to recent rumors circulating in northern Nigeria, where some mothers have refused to permit their children to be vaccinated. According to Kew, the parents have heard that the polio vaccine is a Western plot to sterilize their children. Their resistance to the push for universal vaccination is the reason the country remains a polio hot spot, and the consequences extend beyond its borders. Infections in Nigeria have spread westward to Ghana, the Ivory Coast, Mali and Guinea, and eastward to Sudan, Yemen and Somalia.

Problems getting everyone vaccinated aren't the only factor slowing the eradication campaign. The poliovirus can survive in water or sewage for many days, and a small number of immunocompromised polio patients have excreted live virus for years. That means a community in which no one is currently infected may still harbor active viruses. Worse, live vaccine strains can recover neurovirulence and (even if only rarely) cause paralytic disease. About one in a million people given the live oral virus will develop crippling paralysis.

In recent years, circulating vaccine-derived poliovirus has

produced small outbreaks in areas, including the Dominican Republic and Haiti, where wild poliovirus was thought to have been eradicated. That, Wimmer explains, is because oral Sabin vaccines were originally developed by passing them through a nonhuman host environment: monkey kidney cells. Through natural selection, new strains adapted to that alien environment. Once the vaccine virus finds itself in the human intestine, the weakened viral strains adapt to their new conditions and move closer to the original, virulent wild form. These better-adapted viruses can travel in the community if everyone isn't immunized, sometimes causing paralytic disease. Such dangers posed by oral live vaccines have prompted the United States and Europe to switch to IPV, Salk's original vaccine.

Circulating vaccine-derived polioviruses tend to grow progressively more neurovirulent, though the exact reason is another mystery. Is it a matter of binding more efficiently to the receptors or, as Kew believes, a re-evolution of the vaccine strain's capacity to replicate more effectively—the better to exploit a host's tissues and become more virulent? Does the virus's neurotropism, a tendency to target nervous system tissue, confer any advantage to the virus, or is tropism, and the paralysis it causes, just an incidental effect?

Whether we will ever solve those and all of polio's other mysteries is doubtful: In the world after the disease, most research on live poliovirus will be restricted or banned, which seems a small price to pay for a world free of polio. ■

## → DOSSIER

1. *A History of Poliomyelitis*, by John R. Paul (Yale University, 1971). An indispensable classic, written by a physician who played a major role in fighting epidemics in the mid-twentieth century.
2. *Splendid Solution: Jonas Salk and the Conquest of Polio*, by Jeffrey Kluger (Putnam, 2004). A lively narrative of Salk's early life, research career and sharp rivalry with Albert Sabin, as well as a vivid history of the development of Salk's inactivated vaccine.
3. *Polio: An American Story*, by David M. Oshinsky (Oxford, 2005). Sets the Sabin-Salk rivalry against a broad canvas of polio in America and the terror that the disease induced in ordinary Americans. Oshinsky makes the scientific issues understandable and compelling.